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# Gigantism Associated with McCune-Albright's Syndrome

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**Summary**

The case of a 16 year-old boy with McCune-Albright's syndrome which is rarely accompanied by gigantism was studied endocrinologically.

The stimulation of growth hormone (GH) release by hypoglycemia, the decline of elevated GH by hyperglycemia and a little lower somatostatin like immunoreactivity (SLI) may support abnormalities of hypothalamic function, but the existence of pituitary microadenoma cannot be ruled out because of the paradoxical suppression of GH release by oral administration of bromocriptine (CB-154) and L-DOPA and the stimulation of GH release by intravenous administration of TRH.

**Key-Words:** *Gigantism — McCune-Albright's Syndrome*

## *Introduction*

Sexual precocity is the most common endocrine dysfunction in McCune-Albright's syndrome, which consists of the triad of fibrous dysplasia of bone, endocrine dysfunctions and cutaneous pigmentation, and is more common in girls than in boys (*Lipson* and *Hsu* 1981). This syndrome is rarely accompanied by gigantism (*Lightner, Robert* and *Frasier* 1975; *Joishy* and *Morrow* 1976) and little is known about the dynamics of the growth hormone secretion in this condition. It has been speculated that hypothalamo-pituitary disfunction underlies the endocrine manifestations of McCune-Albright's syndrome (*Hall* and *Warrick* 1972), and the endorgan autonomy (*Danon, Robby, Kim, Scully* and *Crawford* 1975) or a form of multiple endocrine adenomatosis (*DiGeorge* 1975) has also been suggested. Therefore, to examine these hypotheses, we have performed a detailed endocrinological evaluation of a case of McCune-Albright's syndrome associated with gigantism.

## *Case Report*

A 16 yr old male patient (born in full term and normal birth weight (2800 g)) had been noted to be large from infancy (Fig. 1), but otherwise growth and development had been normal until age 9, when he noticed swelling and tenderness of the right tibia. At age 12 he developed a right humerus fracture while throwing a ball. Bilateral coxalgia, right dorsal foot pain and gonalgia appeared at age 15, and a systemic bone disease was suspected by the roentogenological examination. Sexual precocity was not noted and puberty has developed normally. The patient did not complain of headache, visual disturbance, thirst and polydipsia. He was admitted to our hospital for examination.

On physical examination, the patient's height was 187.5 cm (mean ± 2 SD for controls; 163 ± 14.2 cm) (body height of his parents and brother varied from 152 to 160 cm), and he weighed 77 kg (mean ± 2 SD for controls of his age and sex 52.1 ± 13.6 kg). Blood pressure was 130/70 mmHg. His face was distorted by an osseous protrusion on the right forehead. There was irregular pigmentation on the lip and oral mucosa. The thyroid was slightly enlarged. Axillary and pubic hair was normally developed, and testes were of normal size (16 ml) and of normal consistence. Optic fundi and visual fields were normal. Deformity of his extremities and right coxa vara were present. Neurological examinations were negative. Blood counts, urinalysis and concentrations of serum electrolytes were within normal

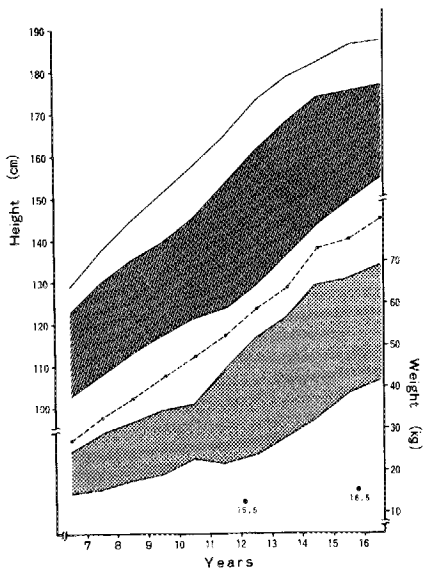


**Fig. 1** Growth curve of the patient. ——: height, --------: weight. Shaded areas show the mean ± 2 SD of the height and the mean ± 2 SD of the weight of normal persons.
•: bone age; 15.5 year-old level at 12.1 year of his age and 16.5 year-old level at 15.7 year of his age.

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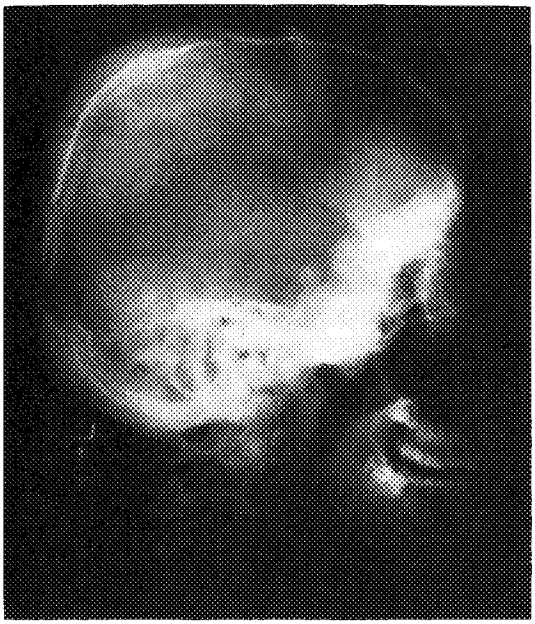

**Fig. 2** Skull showing hyperostosis of the base and the narrowed sella turcica.

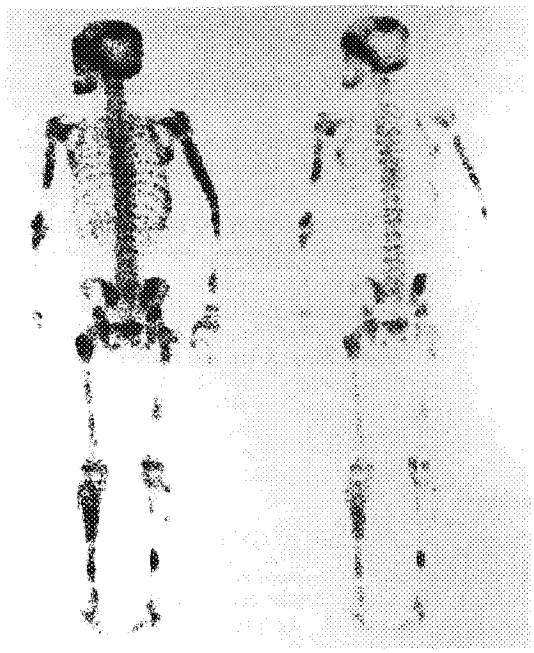

**Fig. 3** $^{99m}$Tc Bone scintigram showing the abnormal accumulation on the skull, humeri, hip bones, femurs and tibiae, etc.

limits (serum Ca: 4.6 mEq/l, P: 4.3 mg/dl). Serum and urinary osmolarities were normal. Abnormal laboratory findings included a slightly increased activity of serum alkaline phosphatase (225.5 mIU/ml; normal value in adult 20–80 mIU/ml, in children 50–220 mIU/ml) and increased urinary excretion of hydroxyproline (190.3 mg/day; normal 15–50 mg/day). The urinary electrolyte excretion was within normal limits. C-reactive protein, rheumatoid arthritis (RA) test and serological test of syphilis (STS) were negative. The liver and renal functions were normal.

X-ray films revealed the bone age corresponded to 15.5 year-old level at his 12.1 year-old of chronological age and 16.5 year-old level at his 15.7 year-old of chronological age. Areas of rarefaction, ground glass-like appearance and cyst-like formation were found in bilateral femurs, humerus, tibiae and iliac bone. The sella turcica was narrowed markedly by the thickened base of the skull (Fig. 2).

$^{99m}$Tc bone scintigram showed abnormal accumulation in the skull, right maxilla, bilateral humerus, bilateral femur and hip bone, etc. (Fig. 3).

Pathological diagnosis for the biopsied femur and iliac bone was polyostotic fibrous dysplasia. Electroencephalogram was within normal limit. Computarized tomogram of the head in a contrast scan showed marked thickening of the base of the skull, but was otherwise normal. Chromosome analysis showed normal male type.

## *Materials and Methods*

### *Specific test procedures*

These were commenced between 0800–0830 h after an overnight fast and 1 h of bed rest. An indwelling catheter was inserted into an antecubital vein and normal saline was infused via the catheter to keep the vein open. After the basal samples were obtained, the following were administered as test procedures: 1) glucose (100 g, orally); 2) crystalline insulin (0.05 u/kg, i.v.); 3) L-Dopa (400 mg, orally); 4) bromocriptine (CB-154; 2.5 mg, orally); 5) propranolol (10 mg, orally) and glucagon (1 mg, s.c.); 6) TRH (500 μg, i.v.); 7) LHRH (100 μg i.v.); and 8) PTH (parathyroid extract; Eli-Lilly, 200 u, i.v.). Venous blood samples were collected as indicated in tables and figures. In case of PTH injection (Ellsworth Howard test), hourly urines were also collected for 2 h before the injection and for 3 h afterwards. Urine samples were analyzed for cyclic AMP (cAMP) and creatinine.

L-Dopa was purchased from Sankyo Co. Ltd., Japan. CB-154 was from Sandoz Co. Ltd., Switzerland. TRH and LHRH were from Tanabe Co. Ltd., Japan. Glucagon and PTH were from Eli-Lilly Co. Ltd., U.S.A. ACTH (Cortrosyn Z) was from Organon Co., the Netherlands.

### *Methods*

Plasma TSH, GH, LH, FSH, ACTH, prolactin (PRL), insulin, calcitonin and cortisol were measured by commercially available radioimmunoassay kit. For ADH determination, ADH was extracted from plasma by adsorption to florisil (*Beardwell* 1971) and then measured by radioimmunoassay using double antibody method. Synthetic arginine vasopressin (Sigma, grade II) was purchased from Sigma Co., U.S.A. and was labelled with Na $^{125}$I. Rabbit antibody to 8-arginine vasopressin was from Calbiochem. Co., U.S.A. This assay system was not interfered with 1-desamino-8-D-arginine vasopressin (3%) and lysine vasopressin (< 1%). Plasma TRH was extracted by 2 ml of ethanol and was dried under a stream of air in a hot water bath (50°C) and then dissolved with saline. The recovery was 80–90%. TRH immunoreactivity in each sample was measured by radioimmunoassay using double antibody technique (*Nihei, Wanibe, Yamauchi, Imai, Kataoka* and *Ishihara* 1977). Rabbit synthetic TRH antibody (titer 1:60,000) did not cross-react with TRH analogues, human pituitary hormones, synthetic LH-RH and prostaglandins. In normal human plasma, the mean value of TRH was 30 pg/ml when undetectable TRH levels were excluded, and the maximal value was 104 pg/ml. The detectable value of TRH

in plasma by this radioimmunoassay was 1.6 pg/ml (*Nihei, Ikeda, Murata, Kamikawa, Suzuki* and *Yamazaki* 1979).

Plasma PTH (iPTH) was assayed by radioimmunoassay using C-terminal PTH as antigen.

The Second International Reference Preparation for Human Menopausal Gonadotropin was used as a reference standard for both LH and FSH.

Urinary and plasma cyclic AMP were determined by radioimmunoassay using dextran coated charcoal (*Nakagawa, Tomita, Uchikawa, Mitsuma* and *Imagawa* 1978).

Plasma somatostatin like immunoreactivity (SLI) (*Chihara, Arimura* and *Schally* 1979) was measured by radioimmunoassay described in detail elsewhere (*Gerich, Greene, Hara, Rizza* and *Patton* 1979).

## *Results*

### *Basal evaluation*

The basal plasma concentrations of GH and somatomedin C were 18.0 ng/ml (normal value: < 5 ng/ml) and 2.4 u/ml (0.36–1.67 u/ml). The basal plasma concentrations of the other pituitary hormones: PRL, ACTH, TSH and ADH, were 16 ng/ml (normal value: 2–20 ng/ml), 56 pg/ml (9AM) (15–85 pg/ml), 4.3 IU/ml (< 12 IU/ml), and 0.5 μU/ml (< 3 μU/ml), respectively. $T_3$RSU was 29.4% (26.6–34.5%); serum $T_3$ and $T_4$ were 1.2 ng/ml (0.96–1.82 ng/ml) and 7.7 μg/dl (5.1–12.8 μg/dl). The titer of thyroglobulin and cytoplasmic antibodies were less than 100 times dilution. Thyroidal $^{131}$I uptake was 4.4% (3 h) and 13.9% (24 h). The thyroidal scintigram showed a uniform uptake scan without any defects. The plasma iPTH concentration was 0.26 ng/ml (normal value; less than 0.5 ng/ml) and that of calcitonin was 24 pg/ml (normal value; less than 300 pg/ml). The urinary excretion of 17 OHCS was 7.9 ± 1.4 mg/day, of 17 KS was 7.7 ± 1.5 mg/day, of adrenaline was 14.9 μg/day (normal value: less than 12 μg/day) and of noradrenaline was 93.4 μg/day (normal value: 10–90 μg/day). The diurnal variation of plasma cortisol showed a normal pattern as follows: 9.6 μg/dl (6 AM), 5.7 μg/dl (12 AM), 3.5 μg/dl (6 PM) and 2.6 μg/dl (12 PM). The urinary excretion of testosterone was 18.6 μg/day (normal value: 12–60 μg/day). The glucose tolerance test showed slightly impaired pattern determined by diagnostic criteria of National Diabetes Data Group (National diabetes data group 1979) (Table 1). This may be due to the excessive secretion of growth hormone.

### *Hypothalamo-pituitary function* (Table 1)

The basal plasma concentration of GH was slightly elevated at each test (10.8–19.8 ng/ml). The plasma GH level was decreased from 19.8 ng/ml to 9.6 ng/ml at 120 min after glucose administration, but failed to suppress to less than 5.0 ng/ml, while it was increased from 10.8 ng/ml to 27.5 ng/ml at 60 min in response to crystalline insulin. However, the plasma GH was minimally affected by the administration of a combination of glucagon and propranolol. Moreover, the plasma GH concentration was reduced from 20.9 ng/ml and 16.8 ng/ml to 8.5 ng/ml and 8.8 ng/ml respectively by CB-154 and L-Dopa (Fig. 4). On the contrary, TRH increased plasma GH from 18.2 ng/ml to 32.0 ng/ml (Fig. 5). Plasma PRL concentration increased from 11.7 ng/ml to 37.3 ng/ml after TRH test (Fig. 5) and decreased from 16.0 ng/ml and 16.3 ng/ml to 6.7 ng/ml and 3.3 ng/ml respectively after L-Dopa and CB-154 administration (Fig. 4). Plasma TSH concentration also increased from 4 μIU/ml to 33 μIU/ml after TRH test. The basal plasma concentration of TRH was 140 pg/ml and that of SLI was 72 ± 7.7 pg/ml (mean ± SE) (normal value: 104 ± 12) which was significantly lower than the normal value ($P < 0.05$). The plasma TRH level was slightly declined at 30 min after the administration of L-Dopa (Table 2). The plasma SLI level was unaffected by the administration of TRH or L-Dopa (Table 3). Urinary excretion of 17 OHCS increase from 7.9 mg/day to 42 mg/day after intramuscular administration of ACTH-Z for 3 days. Administration of metyrapone (Metopirone 3.0 g, orally) increased urinary excretion of 17 OHCS from 9.9 mg/day to 21 mg/day and administration of dexamethasone (2–8 mg/day, orally) suppressed urinary excretion of 17 OHCS from 4.8 mg/day to 1.4 mg/day. The basal plasma concentration of LH and FSH were 7.8 mIU/ml and 10.6 mIU/ml, respectively. Plasma LH and FSH were increased from 7.6 mIU/ml and 10.1 mIU/ml to 50 mIU/ml and 37.5 mIU/ml, respectively, at 90 min in response to LH-RH bolus injection.

**Table 1** Changes of serum GH level to various stimuli

| loading | | min | bef. | 15 | 30 | 60 | 90 | 120 | 150 | 180 | 240 | 300 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 100 glucose p.o. | | GH (ng/ml) | 19.8 | | 15.6 | 11.6 | 10.9 | 9.6 | | 10.3 | 12.0 | 17.3 |
| | | glucose (mg/dl) | 85 | | 164 | 201 | 174 | 154 | | 122 | 78 | 82 |
| | | IRI (mIU/ml) | 9.6 | | 54 | 48 | 40 | 50 | | 53 | 12 | 10.5 |
| 4 u. regular insulin i.v. | | GH (ng/ml) | 10.8 | 13.0 | 9.6 | 27.5 | 23.4 | 15.9 | | | | |
| | | glucose (mg/dl) | 84 | 40 | 68 | 80 | 82 | 86 | | | | |
| | | ACTH (pg/ml) | 10 | | 10 | 44 | | 10 | | | | |
| Glucagon 1 mg i.m. | | GH (ng/ml) | 14.0 | | 12.2 | 13.7 | 14.7 | 13.1 | 14.4 | 18.0 | | |
| propranolol 10 mg p.o. | | glucose (mg/dl | 91 | | 173 | 179 | 131 | 96 | 79 | 82 | | |
| 6 months later | 100 g glucose p.o. | GH (ng/ml) | 15.8 | | 13.6 | 16.6 | 14.7 | 14.5 | 16.0 | 14.9 | | |
| | 4 u. reg. insulin | GH (ng/ml) | 12.5 | | 13.0 | 10.9 | 12.6 | 13.6 | | 13.7 | | |

(Normal value of GH: < 5 ng/ml, ACTH (8:00–10:00 a.m.): 15–84 pg/ml, IRI (fasting): 7–24 μU/ml, glucose (fasting): 60–110 mg/dl)

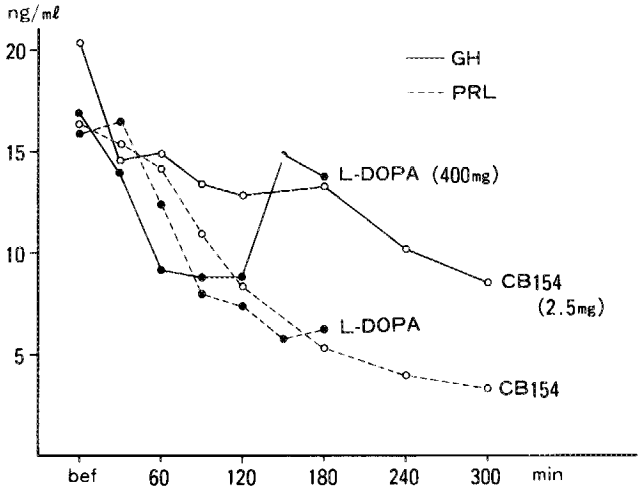


**Fig. 4** Responses of GH secretion to L-DOPA or CB-154 administration. Both agents suppressed serum GH level as well as serum PRL level. 400 mg of L-DOPA or 2.5 mg of CB-154 was administered orally.

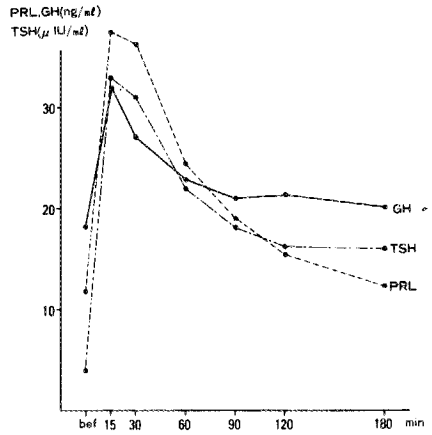


**Fig. 5** TRH test (500 μg of TRH was injected into cubital vein). GH secretion was mildly stimulated by TRH. Serum TSH and PRL level was elevated by TRH.

**Table 2** Effect of TRH and L-DOPA on serum TRH level (pg/ml)

| loadings | bef. | 15′ | 30′ | 60′ | 90′ | 120′ | 150′ | 180′ |
|---|---|---|---|---|---|---|---|---|
| TRH 500 μg i.v. | 140 | 1100 | 640 | 240 | 110 | 130 | | 85 |
| L-DOPA 400 mg p.o. | 160 | 130 | 84 | 140 | 175 | 162 | 160 | 150 |

(Normal value of serum TRH is described in the text)

**Table 3** Effect of TRH, L-DOPA, glucose and insulin on serum somatostatin like activity (SLI)

| loadings | bef. | 15′ | 30′ | 60′ | 90′ | 120′ | 150′ | 180′ |
|---|---|---|---|---|---|---|---|---|
| TRH 500 μg i.v. | 62 | 54 | 50 | 71 | 70 | 65 | — | 50 |
| L-DOPA 400 mg p.o. | 66 | — | 105 | 75 | 70 | 53 | — | 52 |
| glucose 50 g p.o. | 65 | — | 83 | 83 | 75 | 70 | 60 | 78 |
| reg. insulin 4u. i.v. | 95 | 90 | 92 | 115 | 83 | 111 | — | — |

(Normal value of serum SLI: 104 ± 12 (mean ± SE) (n=17))

The urinary excretion of phosphorus was increased from 3.8 mg/h to 10.5 mg/h and that of cyclic AMP was also increased from 500 ng/h to 11,518 ng/h at 60 min in response to PTH administration. The increase of plasma cyclic AMP (24.3 pg/ml to 87.6 pg/ml) provoked by PTH was also observed at 30 min (Ellsworth-Howard test).

Six months later, glucose and insulin tolerance tests were repeated. At this time the plasma GH concentration was unaffected by hyper- or hypoglycemia (Table 1).

At the present time, the serum GH concentration in this case is well controlled by the oral administration of 2.5 mg CB-154.

## *Discussion*

The etiology of McCune-Albright's syndrome has not been established. Albright suggested dysfunction of the hypothalamo-pituitary neurohumoral pathway in this syndrome (*Albright* and *Reifenstein* 1948).

*Hall* and *Warrick* proposed the thesis that all of the endocrine manifestations result from the hypersecretion of hypothalamic releasing hormones (*Hall* and *Warrick* 1972), and abnormally high sensitivity to trophic hormones was suggested by *Scully* and *McNeely* (1975).

On the other hand, *Danon* et al. (1975) suggested the autonomous hypersecretion of endorgans and *DiGeorge* (1975) proposed that it may be a form of multiple endo-

crine adenomatosis. This syndrome is rarely accompanied by gigantism or acromegaly (*Scurry, Bicknell* and *Fajans* 1964; *Lightner, Robert* and *Frasier* 1975; *Scully* and *McNeely* 1975; *Joishy* and *Morrow* 1976; *Carr, Mathie, Manners* and *Colman* 1979; *Lipson* and *Hsu* 1981; *Higashihara, Takano, Murase, Murakami, Sasaki, Ishibashi, Yamaji, Osawa* and *Kosaka* 1982).

The case reported by *Scurry, Bicknell* and *Fajans* (1964) was considered to have pituitary tumor by polytomography of the sella, the case of *Lightner, Robert* and *Frasier* (1975), *Lightner, Penny* and *Frasier* (1976) was found to have eosinophilic pituitary adenoma, and the case of *Joishy* and *Morrow* (1976) was due to chromophobe adenoma. The most recently reported case by *Lipson* and *Hsu* (1981) was found to have a pituitary and suprasellar mass and was effectively treated by 5000 rads of external radiotherapy to the sella and suprasellar regions. In these reports, serum GH concentration was greater than 80 ng/ml and was not suppressed by glucose administration.

In the present case, the elevated level of fasting serum GH was decreased from 19.8 ng/ml to 9.6 ng/ml at 120 min during an oral glucose tolerance test and serum GH release was normally stimulated by hypoglycemia induced by intravenous administration of insulin. Glucose is supposed to act through specific receptor in the hypothalamus (*Blanco, Schlach* and *Reichlin* 1966). Therefore, the responses of plasma GH to changes in plasma glucose concentrations suggest that the pituitary response is controlled by hypothalamic stimuli. Furthermore, we observed slightly elevated TRH level and a little lower SLI level in plasma. These evidences may have some connection with abnormalities of hypothalamic function which induce serum GH level elevated. However, SLI in peripheral blood appears to be attributable to the secretion from the gastrointestinal tract and/or pancreas (*Hermansen* 1980; *Schusdziarra* 1980). The contribution of somatostatin released from the hypothalamus to the peripheral blood has not been determined yet.

In this patient, the sella turcica was markedly narrowed by the thickened base of the skull and neither tomography nor computarized tomography of the head could detect pituitary or suprasellar mass, suggesting that the hypersecretion of GH is caused by long standing hypothalamic stimuli which may induce the release of growth hormone releasing factor rather than a rapidly growing pituitary tumor.

However, intravenously administered TRH stimulated GH release, and both CB-154 and L-DOPA suppressed the release of GH in this patient. TRH or dopaminergic drugs may act at the hypothalamus or may influence GH release by a direct action on the pituitary. *Ishibashi* and *Yamaji* (1978) showed that both TRH and CB-154 possess a direct action on pituitary adenoma cells of acromegaly and that aberrant GH responses to TRH and dopaminergic agonists in acromegalic patients may be explained by the altered cellular membrane receptors of the adenoma of these subjects. Clinically, these paradoxical responses of GH are shown to be normalized after selective hypophysectomy in some cases of acromegaly (*Hoyte* and *Martin* 1975; *Samaan, Leavens* and *Jesse* 1974). In our case, the unresponsiveness to hyperglycemia or hypoglycemia which appeared 6 months after the first examinations may be suggesting the autonomous secretion of GH from the developed microadenoma in the pituitary gland. Therefore, the existence of a microadenoma of the pituitary gland in the present case cannot be excluded.

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